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CoQ_{10}-CONTAINING PRELIPOSOMES AND PREPARATION THEREOF

Field of the ~~Of The~~ Invention

The present invention relates to the fields of pharmaceutics and cosmetics. More specially, the present invention relates to CoQ_{10}-containing preliposomes, and more particularly, relates to the preparation method and the application of CoQ_{10}-containing preliposomes which contain spongiamine.

BACKGROUND of the Invention

CoQ_{10} (conenzymeQ_{10}, ubidecarenone) is a kind of a liposoluble quinine compound, which has the same character as a vitamin. The prominent function of CoQ_{10} is anti-oxidation and cleaning free radicals. CoQ_{10} is one of the most important functional components used in many anti-aging products at present. It has been proved experimentally that CoQ_{10} can accelerate the metabolism of skin, accelerate the transport of cellular respiration chain and ATP production of facial and hand skin. Simultaneously, CoQ_{10} can inhibit oxidation of the skin lipid, and consequently nourish and activate the skin. It is reported that body slimming lotions and UV expert creams which contain CoQ_{10} have obvious effects on preventing the formation of furrows, whitening the complexion, increasing the elasticity of the skin and so on. CoQ_{10} not only protects the skin, but also prevents and cures skin diseases of human beings. It has been experimentally proven that CoQ_{10} has obvious therapeutic effects

on photoallergy, dermatitis, hair-lose, bedsores, ulcers, wounds of the skin, hyperpigmentation and so on. Because the molecular structure of CoQ_{10} has an unsaturated double bond, CoQ_{10} is extremely unstable and is easy to oxidize and becomes decomposed by the oxygen and light in the air. In addition, heating or contacting CoQ_{10} with metal ions will accelerate its decomposition As a result, the content of CoQ_{10} in products becomes decreased, and the activity of CoQ_{10} is quickly lost, adversely affecting the quality and actual effect of the products. In addition, CoQ_{10} is a liposoluble compound, which makes it difficult to mix with the water-soluble cosmetics. The foregoing disadvantages of CoQ_{10} extremely restrict the development and application of CoQ_{10}.

Liposomes are composed of hydrophilic bursa bubbles which consist of lecithoid double molecular layers. Liposomes have characteristics that improve the stability of drug encapsulation, facilitate the percutaneous absorption of drugs, prolong the time of drug action, control the drug targeting at local pathological parts of the body, and decrease the side effects of drugs. Thus, as drug carriers, liposomes have been widely used in pharmaceutics and cosmetics. CoQ_{10} liposomes could improve the stability of drugs, facilitate the percutaneous absorption of drugs, and increase the water-solubility of drugs. But generally being a kind of liposome suspension solution, CoQ_{10} has obvious shortcomings in the stability. The reasons are as following:

1. As colloidial particulates, liposomes are a kind of unstable thermodynamic system which is easy to congregate, fuse and sedimentate, and the oxidation decompose of the lecithoid causes leakage of the encapsulation drug into the

aqueous solution, etc., resulting in the instability of the liposome.

2. The instability of the structure of CoQ_{10} makes drugs more instable in the water.

3. The ratio of CoQ_{10}, liposome suspension and drug content is generally fixed; however, the required content of CoQ_{10} differs in different cosmetics. Thus, it is not convenient to mix CoQ_{10} liposome suspensions with cosmetics which contain CoQ_{10}.

So it is necessary to find a kind of liposome preparation which is convenient, flexible, easy to mix with cosmetics which contain CoQ_{10}, in order to make the liposomes and drugs more stable, and storable for a long periods of time.

Disclosure of the Invention

An object of present invention is to overcome the shortcomings of CoQ_{10} and common CoQ_{10} liposome, and to supply a kind of CoQ_{10}-containing preliposomes which contain spongiamine. The present invention will increase the stability of CoQ_{10} and liposomes and make the mixing of cosmetics more flexible and convenient.

The CoQ_{10}-containing preliposomes made according to the present invention are a kind of solid preparation which are the granular and lyophilized. Before using, water is added to the CoQ_{10}-containing preliposomes. After hydration and surging, the CoQ_{10}-containing preliposomes can become CoQ_{10}-containing liposomes.

The structure of the CoQ_{10}-containing preliposomes of the present invention contain spongiamine at a concentration at 0.1% ~ 20% (W/W). Spongiamine can

further facilitate the percutaneous absorption and improve the effect of CoQ_{10} in cosmetics.

The CoQ_{10}-containing preliposomes which contain spongiamine according to the present invention are prepared by the following methods and processes.

1) CoQ_{10}, spongiamine and other lipid components are melted by heating or are dissolved by proper organic solvent(s) so that a lipid solution is made,

2) A fluidized bed can be used to spray the above-mentioned lipid solution on an underlay which is suspended in the middle of the fluidized bed. The organic solvent is volatilized, and CoQ_{10}-containing preliposomes which contain spongiamine is obtained,

3) Make the lipid solution mentioned in step 1) and water solution which contains an underlay by known methods such as a membrane dispersion method or a melt method or an infuse method to obtain CoQ_{10}-containing liposomes which contain the underlay,

4) Make the CoQ_{10}-containing liposomes which contain an underlay by freeze drying or spray drying, or wiping off the moisture to obtain CoQ_{10}-containing preliposomes which contains spongiamine.

The CoQ_{10}-containing preliposomes of the present invention contain CoQ_{10} at a concentration at of 0.2 ~ 40% (W/W). After restoring by adding water, the concentration of the CoQ_{10} is 0.1 ~ 20% (W/W).

Suitable organic solvents that can be used according to the present invention include dichloromethane, trichloromethane, ether and ethanol.

The concentration of underlay used according to the present invention involved in the CoQ_{10} preliposomes which contain spongiamine is 1~80%.

Underlays that can be used according to the present invention are selected from one of the following materials: mannitol, glucose, sorbitol, sucrose, lactose, fucose, sodium chloride and polyvinylpyrrolidone.

The lipid components that can be used according the present invention include spongiamine and at least one of the following components: cholesterol, soy lecithin, yolk lecithin, hydrogenated lecithin, DSPC, DPPP, poloxamer, DMPC and non-ionic surfactant like Brij.

The materials used ~~in~~ according to the present invention are all commercially available.

The CoQ_{10}-containing preliposomes which contain spongiamine according to the present invention not only have the same merit as the common liposomes in that they increase the stability of the drugs, facilitate the percutaneous absorption of drugs, and prolong the time of drug action. In addition, the CoQ_{10}-containing preliposomes which contain spongiamine according to the present invention have the following merits:

1. The increased stability of CoQ_{10}-containing liposomes allow for longer storage times.

Because the <u>the</u> preliposomes are solid drugs, they overcome the shortcomings that the common liposomes have, such as congregating, sedimentating, fusing, leaking and so on.

2. The stability of the CoQ_{10} is increased.

Because the the preliposomes are solid drugs, the present invention can be used to make unstable more stable in the solid state than in the liquid state.

3. The percutaneous absorption of the CoQ_{10} is increased.

The structure of the liposomes containing spongiamine according to the present invention facilitate the percutaneous absorption of drugs.

The CoQ_{10}-containing liposomes of the present invention can be mixed with other components at at random making them easier and more convenient to formulate into cosmetics.

Generally, for cosmetics which contain liposomes there is a certain range of the liposome volume. If the contains of liposomes exceed the range, characteristics of the cosmetics will be affected, such as viscosity, flow property, viscosity, the content of the active component and so on. Furthermore, certain cosmetics require different amounts of the CoQ_{10}. Before use, water can be added to the CoQ_{10}-containing preliposomes which contain spongiamine according to the present invention on demand, so as to provide liposomes which have different drug contents to meet different cosmetic prescriptions.

Examples

Example 1:

In this example, 120g of CoQ_{10}, 50g of spongiamine, 50g of yolk lecithin, 100g of cholesterol, 100g of sucrose, were combined with enough PBS (pH 7.4) to produce

a volume of 1000 ml.

The CoQ_{10}, spongiamine, yolk lecithin and cholesterol from the above prescription were put into a triangle flask, heated to cause fusion, and stored in a water bath at 80°C for further use. 800 ml of PBS (pH 7.4) was used to dissolve the 140g of sucrose. The dissolved solution was filtered and heated in a water bath to reach the same temperature with the liposome solution. The sucrose solution was mixed with the liposome solution by surging and cooled. Enough PBS (pH 7.4) was added to produce 1000 ml of the mixed solution. A high pressure homogeneous management (50 MPa of high pressure, 10 MPa of low pressure) was used to obtain a liposome suspension solution. After spray drying, a fluid CoQ_{10}-containing preliposomes which contained spongiamine was obtained.

Example 2:

In this example, 30g of CoQ_{10}, 50g of spongiamine, 30g of soy lecithin, 100g of cholesterol, 40g of poloxamer F_{68}, 200g of glucose, and 200 ml of chloral, were combined with enough PBS (pH 7.4) to produce a volume of 1000 ml.

The CoQ_{10}, spongiamine, soy lecithin, poloxamer F_{68} and cholesterol from the above prescription were put into a 1000 ml rocked flask and the chloral was used to dissolve the lipid components. The resulting mixture was subject to membrane evaporation in a water bath at 25~40°C to make the lipid form a membrane layer at the bottom of the rocked flask. ~~Use~~ 800 ml of PBS (pH 7.4) was used to dissolve the 200g of glucose. The solution was filtered and added to the flask containing the lipid

membrane for hydration thereof using surging. Enough PBS (pH 7.4) was added to produce 1000 ml of mixed solution which was subject to ultrasonic treatment (output 4, duty cycle 50%, time 10 mins) to produce a liposome suspension solution. After freeze drying (temperature at -50°C the degree of vacuum is 50 millitorr), a kind of loose CoQ_{10}-containing preliposomes which contain spongiamine was obtained.

Example 3:

In this example, 50g of CoQ_{10}, 50g of spongiamine, 60g of hydrogenated lecithin, 40g of cholesterol, 50g of poloxamer F_{68}, and 80g of fucose, 200ml of ether, were combined with enough PBS (pH 7.4) to produce a volume of 1000 ml.

The CoQ_{10}, spongiamine, hydrogenated lecithin, poloxamer F_{68} and cholesterol from the above prescription were put into a 500ml of triangle flask and the ether was added to dissolve the lipid components for further use. 800 ml of PBS (pH 7.4) was used to dissolve the 80g of fucose. The fucose solution was filtered and put into the triangle flask which was stored in a water bath at 30~60°C, and mixed round by magnetic force at the speed of 200~1000 rpm. After the organic solvent was evaporation a liposome suspension solution was obtained and freeze dried (temperature at -50°C, the degree of vacuum is 50 millitorr) to produce a kind of loose CoQ_{10}-containing preliposomes which contain spongiamine.

Example 4: test of stability

Samples of the three batches of CoQ_{10}-containing preliposomes which contain

spongaimine and a common CoQ_{10}-containing liposomes (the liposomes suspension before drying) were stored separately at a temperature of 40°C and at a relative humidity level of 75%. After 0, 1, 2 and 3 months, High Performance Liquid Chromatography (HPLC) was used to test the content of CoQ_{10} in the preliposomes and the common liposomes. The content of 0 month CoQ_{10} in the preliposomes and the common liposomes was used as 100% to compare the content of drug at other times with the above mentioned content of CoQ_{10}, and calculate the percent content of drug as the time goes by.

Table 1 lists the stability comparing results of the content of CoQ_{10} in the preliposomes and the common liposomes.

Table 1

	The change percent of the content of CoQ_{10} (%)			
Time (mo)	0	1	2	3
Common liposomes	100.00	93.32	88.03	83.50
Preliposomes	100.00	99.86	99.53	98.76

The results show that the content of the drug contained in the common liposomes decreased along with the time while the content of the drug contained in the preliposomes did not decrease along with the time significantly. This indicates that the CoQ_{10}-containing preliposomes which contain spongiamine could evidently improve the stability of drugs.